Testimony

of

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before the

Subcommittee on Oversight and Investigations
of the
Committee on Energy and Commerce

House of Representatives

On

Science and Mission at Risk:
FDA's Self Assessment

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Chairman Dingell and members of the committee,

My name is Garret FitzGerald. I am a Professor of Medicine, Chair of Pharmacology and Director of the Institute for Translational Medicine and Therapeutics at the University of Pennsylvania. I have worked on basic and clinical aspects of drug action for 30 years.

The FDA is charged with a mission fundamental to the safety of the nation. Recent events – the cardiovascular hazards of COX-2 inhibitors; the uproar over the antidiabetic drug, Avandia and the confusing and contradictory messages in the press about the safety

of the lipid lowering drug, Vytorin, have undermined our belief that the Agency can safeguard the public and communicate informed and unbiased information about drug safety.

The recent episodes of pet food and toothpaste contamination, remind us that bulk production of the drugs, chemicals and cosmetics that reach the US has largely moved offshore.

Serious as each of these incidents is, they are merely warning signs of a gathering storm. We ignore them at our peril. The FDA is the safeguard for integrity of our drug supply and our food supply. Failure of the FDA to fulfill its mission would expose each and every one of us to danger, either from the willful intent of terrorists or the incompetence of manufacturers.

Both the IOM report on "The Future of Drug Safety"[1] and our Subcomittee's report, "FDA Science and Mission at Risk"[2] have

identified in plain terms a disturbingly systemic set of problems in the Agency.

These include the politicization and instability of leadership, attrition of manpower, poor morale, structural and organizational inadequacies, depleted infrastructure and – most importantly- critical gaps in scientific expertise and technology as emphasized in our Science Board report.

These factors – many, but not all reflecting a serious erosion of necessary resource - compound to undermine seriously the science base of the Agency and its ability to fulfill its mandate.

How have we let the FDA reach this point?

We have failed to maintain and upgrade the FDA over the past 50 years. Complex organizations, just like complex machines –planes

are a good example – can continue to function effectively if preventively and reactively maintained.

Last year a 57 year old seaplane lost a wing and fell into the sea killing all 20 people aboard. It had been poorly maintained; literally, papering over the crack. However, the National Transportation Board assigned blame not just to the airline, but also to the Federal Aviation Agency – for not amending their rules with the times and having the appropriate regulatory requirements in place.[3]

How can we move to restore the ability of the Agency to face the challenges of the world in 2008, rather than those of 1958?

We must empower the FDA to cope with the rapidly changing science of drug development to ensure a pipeline of safe, innovative and effective medicines for our present and our future. As Dr. Cassell emphasized in her opening remarks, there have

been major scientific advances in drug discovery over the past decade, yet the way in which FDA reviews drugs and steers their development has not changed in over half a century.

Firstly, we must reorganize the structure of science at the FDA. Unlike many agencies, this one must be grounded in science and science must permeate its activities and decisions. Amazingly, FDA presently lacks a Chief Scientific Officer. We believe that such a position of leadership is necessary to guide the restructuring of the Agency and provide constant advice to the Commissioner.

As Dr. Cassell emphasized in her opening remarks, the FDA does not subscribe to rigorous peer review of their scientific programs and centers. Again, as she said, to our knowledge the Center for Drug Research and Evaluation and the Office of Regulatory Affairs have never been peer reviewed in their totality. Those

centers that have been peer reviewed have been so infrequently and not in a formal process.

Secondly, Agency scientists need to become re-engaged with the scientific community, through attendance at meetings and encouragement to publish on regulatory science and training.

Third, the presently segregated approaches to drug review and evaluation before and after approval for marketing must be integrated. Our information about how a drug works and how safely it works is fragmentary at the time of approval; we must exploit enhanced mega databases of clinical information, accessed in real time by Agency scientists to assess drug safety post approval. You will hear more about this in Dr. Nordenberg's testimony.

It took 7 years from when we first predicted that Vioxx and Celebrex would cause heart attacks for the evidence to accumulate

and this message to be delivered in unequivocal terms to consumers. This reflected a failure to integrate different types of scientific information and a reliance on passive surveillance for safety signals once these drugs reached the market. We must and we can do better.

Fourth, Agency scientists may indeed be suspicious of safety signals, but lack the freedom, the expertise and often the site where confirmatory tests might be pursued. We believe that the FDA needs access to a neutral testing ground –a “Jet Propulsion Lab”.

What is a JPL? When Boeing comes to the Department of Defense with a new engine for jet fighters, DOD doesn’t say, “wonderful, let’s write you a check”. They may not have the facilities or the expertise to put it through its paces in Washington, but they can turn to their collaborating experts at the JPL in Pasadena and subject it to rigorous assessment. The JPL provides a

technologically advanced site for assessment, independence and expertise.

This is the model we need for the FDA – academic sites where they might interact with experts in these emerging sciences to pursue evidence that is important to the regulators to clarify drug safety or efficacy both before and after drug approval.

Presently, we approve drugs based on the ability to detect large average effects of benefit or risk in studies of large populations. This approach is clearly inadequate and essentially unchanged for the past 50 years.

However, people vary strikingly in their response to most drugs – differences determined by the interaction of factors within their environment and their individual complement of genes. What matters most to people is not whether there is an average effect in a population, but how a drug will work in them.

The FDA is poorly placed to react, either to the challenges or the opportunities of this revolution in technology and medicine. Again, as pointed out by Dr. Cassell, our Subcommittee found that the development of medical products based on “new science” cannot be adequately regulated by the FDA.

Information from these new sciences is already providing an understanding of biological “networks” which, just as the interstate superhighway system lets us navigate the country, will allow us to understand more comprehensively how our body works in health and how and where these highways are blocked in disease.

The FDA is not on this superhighway; it is stuck on a rural dirt track trying to get from place to place in a Model T. It needs a major infusion of resource to give it modern, fuel efficient cars and to get them on that superhighway; it also needs the drivers who can cope with the traffic and roads of the 21st century. We propose that

it hires some drivers, but gets up to speed by renting the rest, part time, from the scientific fast lane – the academic sector.

It is unrealistic – short of the reintroduction of the military draft - to believe that the Agency could ever recruit a sufficient number of individuals skilled in these emerging sciences to assess and interpret the information from these new sciences.

The inability of FDA scientists rigorously to review these products will not only result in lost lives in some cases, but in others it will result in the failure of critical, innovative, life-saving medicines to reach the bedside in a timely manner. Failure of the FDA to advance to the 21st Century will have a major negative impact on the U.S. economy and the threatened pre-eminence of the U.S. in biotechnology and the biomedical and agricultural sciences.

For example, the only relevant expertise that the Agency has in house in genomics- the most advanced of the new sciences - is fragmented, uncoordinated and paltry.

By comparison, the FBI has invested millions of dollars in genomics and the NIH has an entire Institute of Genome Sciences. Even the CDC has made remarkable advances in applying genomics in multiple areas of public health, including food borne diseases. Likewise, USDA is more advanced in this area due to its own investment, but also its interactions with the National Science Foundation and the Department of Energy.

Sadly, the FDA lags far behind its sister agencies and is slowly playing catch up. It should be leading the way and setting the standards in applied genomics. Importantly, expertise in every other aspect of the emerging sciences is essentially nonexistent within the FDA.

Our Subcommittee concluded that science in the FDA is indeed in a precarious state. Because, as Dr. Cassell has emphasized, every regulatory decision that FDA makes is based upon science, this deficit must be addressed.

It is realistic and desirable that the Agency recruits or retrains a small *cadre* expert in the emerging sciences; however, their impact can be magnified if they are integrated into a larger network, a consortium of extramural scientists at academic sites - a Jet Propulsion Lab for the FDA.

Besides amplifying the science base of the Agency in the area of its greatest weakness, this JPL would provide a site in which the Agency expands its capacity to assess medicines using the most modern technologies and a framework for educational exchange. This initiative should also revolutionize our approach to drug development, hastening the time to drug approval and detecting more efficiently and faster problems with drug safety.

This initiative will empower the Agency by harvesting the talent of the US academic sector - the largest biomedical and bioengineering enterprise in the world and one funded largely by the taxpayer.

In summary, we concluded that the FDA is in crisis. Its ability to fulfill its mandate has eroded to a critical degree and will rapidly deteriorate unless they are provided appropriate resources and the Agency takes radical action.

Both the IOM and Science Board reports identify steps that will enhance greatly the ability of the Agency to guarantee the safety of the food we eat and the drugs and devices that we are prescribed. This will require provision of a substantial increment in resources.

However, best to do this while the levees are leaking rather than after the hurricane has hit.

1. IOM. The Future of Drug Safety. Promoting and Protecting the Health of the Public. Committee on the Assessment of the US Drug Safety System, Alina Baciu, Kathleen Stratton, Sheila P. Burke, Editors. The National Academies Press, Washington D.C. 2007 pp 1 -

2. http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4329b_02_01_FDA%20Report%20on%20Science%20and%20Technology.pdf

3.http://www.nytimes.com/2007/05/31/us/31crash.html?scp=2&sq=florida+and+plane+crash+and+wing&st=nyt